REMARKS

Claims 1-125 are pending. Claims 23-26, 29-32, 34-37, 49-52, 64-67, 79-82, 94-97, and 109-112 are amended herein to correct typographical errors. Claims 68 and 98 are amended herein to depend from claim 38. Claims 27, 28, and 38 are amended herein to include the term "detoxified." Support for the amendments can be found throughout the specification, specifically, at least at page 3, lines 22-28; page 4, lines 3-7; and page 15, lines 1-6. No new matter is entered by way of the amendments. Claims 1-125 are pending and under consideration.

RESPONSE TO RESTRICTION REQUIREMENT

In response to the Office Action mailed March 3, 2009, Applicants elect Group I, drawn to a detoxified pneumococcal neuraminidase or antigenic portion thereof, which encompasses claims 1-19. The election is made with traverse.

The Examiner alleged on page 3 of the Office Action that the inventions listed in groups I-XIV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding technical features. WO 02/077021 discloses antigenic fragments of pneumococcal neuraminidase and their potential for therapeutic benefit. Thus, the Examiner argues that the claims lack a special technical feature over the prior art. First, Applicants note that when making a restriction requirement under the unity of invention standard, "the examiner must (1) list the different groups of claims and (2) explain why each group lacks unity with each other group (i.e., why there is no single general inventive concept) specifically describing the unique special technical feature in each group." M.P.E.P. 1893.03(d). The Examiner has failed to explain why each group lacks unity with each other group, and, thus, the restriction requirement is improper.

Second, Applicants maintain that the claims are drawn to a special technical feature, i.e., the *detoxified* neuraminidase, which is novel and inventive over WO 02/077021. As described in the current specification at least at page 45, lines 5-16, pneumococci NanA mutants were recovered from tissues in far fewer numbers than wildtype pneumococci. These findings demonstrate that nasal carriage is a prerequisite for more invasive disease and that "interventions

capable of reducing carriage, such as immunization with NanA, will offer protection against pneumonia, meningitis, otitis-media, and sepsis." See page 45, lines 13-16. To further support this argument, enclosed is an abstract by Dr. James Watt, Dr. Fredrik van Ginkel and Dr. David Briles, inventors of the present application, presented at the 6th International Symposium on Pneumococci and Pneumococcal Diseases, June 8-12, 2008. The abstract states that "NanA-mediated immune protection against colonization does not require an enzymatically active neuraminidase." Therefore, there is a technical advantage to using the detoxified pneumococcal neuraminidase to provide immune protection as described in Example 2 of the specification. As such, the detoxified pneumococcal neuraminidase of the present application has novelty and inventive step over WO 02/077021 and constitute a novel technical feature.

Further, Applicants assert that the claims should have been divided into four groups, at most. (1) Group A, claims 1-19, 27-45, 68-75, and 98-105 (corresponding to Groups I, III, IV, VII, and XI) directed to detoxified pneumococcal neuraminidase and compositions comprising detoxified pneumococcal neuraminidase; detoxified pneumococcal neuraminidase and phosphocholine; and detoxified pneumococcal neuraminidase and a non-phosphocholine antigentic portion of pneumococcal teichoic acid; and methods of prevention or reduction of pneumococcal nasal carriage or pneumococcal infection with detoxified pneumococcal neuraminidase. (2) Group B, claims 20-26, 46-52, 61-67, 76-82, 91-97, and 106-112 (corresponding to Groups II, VI, VIII, X, and XII) directed to methods of generating antibodies to detoxified pneumococcal neuraminidase; phosphocholine; detoxified pneumococcal neuraminidase and phosphocholine; non-phosphocholine antigenic portion of pneumococcal teichoic acid; and detoxified pneumococcal neuramindase and the non-phosphocholine antigenic portion of pneumococcal teichoic acid. In Group B, the Examiner could have further directed the Applicants to elect a species to which antibodies would be generated against (i.e. detoxified pneumococcal neuraminidase, phosphocholine, etc). (3) Group C, claims 53-60 and 113-125 (corresponding to Groups V, XIII, and XIV) directed to compositions of phosphocholine and phosphocholine antibodies and methods of reducing or preventing pneumococcal nasal carriage with phosphocholine antibodies. (4) Group D, claims 83-90 (corresponding to Group IX)

directed to compositions of non-phosphocholine antigenic portion of pneumococcal teichoic acid. Applicants note that Unity of Invention exists when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The claims as set forth into Groups A-E above have a single general inventive concept. For example, the single general inventive concept of Group A is the detoxified pneumococcal neuraminidase and compositions comprising the detoxified pneumococcal neuraminidase. Independent claims 68 and 98 have been amended to depend from claim 38. Specifically, claim 68 has been amended to recite that the composition of claim 38 further comprises a phosphocholine or an antigenic portion thereof of pneumococcal teichoic acid or pneumococcal lipoteichoic acid. Claim 98 has been amended to recite that the composition of claim 38 further comprises a non-phosphocholine antigenic portion of pneumococcal teichoic acid or pneumococcal lipoteichoic acid. Therefore, claims 1-19, 38-45, 68-75, and 98-105, as amended, have unity of invention. Since Applicants elected Group I, at a minimum, Applicants request Groups I, IV, VII, and XI be examined together.

In summary, Applicants assert the restriction requirement is improper and unfairly burdens the Applicants at least because the Examiner failed to explain why each group lacks unity with respect to the other groups, there is a special technical feature that is novel and inventive over the prior art, and because the claims should have been divided into fewer groups. Therefore, Applicants request withdrawal of the restriction requirement. Alternatively, Applicants request that Groups I, IV, VII, and XI be examined together.

Applicants reserve all rights in these claims to file divisional and continuation patent applications drawn to non-elected subject matter or claims.

The absence of a comment regarding the office action does not signify agreement with or concession of any characterization or requirement. In addition, because the arguments and comments herein may not be exhaustive, there may be additional arguments and comments that have not been expressed.

No fees are believed to be due. However, please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: April 3, 2009

Tiffany B. Salmon, Ph.D.
Reg. No. 55,589

1180 Peachtree Street, N.E., 21st Floor
Atlanta, GA 30309
Telephone: (404) 892-5005
Facsimile: (877) 769-7945

12091938.doc

ISPPD-6

6th International Symposium on
Pneumococci and Pneumococcal Diseases
8–12 June 2008, Reykjavik, Iceland

Final program

P3-016 **Anti-pneumococcal seroprevalence, and pneumococcal carriage and meningitis in Burkina Faso, 2006–7**

Judith Mueller[1], Seydou Yaro[2], Berthe-Marie Njanpop-Lafourcade[1], Aly Drabo[2], Serge Diagbouga[2], Régina Idohou[1], Oumarou Sanou[1], Mathilde Lourd[1], Boubakar Nacro[3], Alain Hien[4], Dominique Niamba[5], Sita Kroman[1], Yves Traoré[6], Lassana Sangaré[2], Jean-Louis Koeck[4], Raymond Borrow[7], Bradford Gessner[1]

[1]*Agence de Médecine Préventive, PARIS, France*
[2]*Centre Muraz, BOBO-DIOULASSO, Burkina-Faso*
[3]*Centre Hospitalier Universitaire Sanou Souro, BOBO-DIOULASSO, Burkina-Faso*
[4]*Université de Ouagadougou, OUAGADOUGOU, Burkina-Faso*
[5]*Centre Hospitalier Universitaire Yalgado Ouédraogo, OUAGADOUGOU, Burkina-Faso*
[6]*HIA-Robert Piqué, BORDEAUX, France*
[7]*Health Protection Agency, MANCHESTER, United Kingdom*

P3-017 **Neuraminidase A (NanA) is essential for nasal colonization of mice with *Streptococcus pneumoniae* and recombinant enzymatically active or inactive NanA elicits almost complete protection against nasal colonization of mice**

David Briles[1], Muneki Hotomi[2], Rafia Razzaque[1], Shaper Mirza[1], James M Watt[1], Kristopher Genschmer[1], van Ginkel Fredrik W[3], Susan K Hollingshead[1]

[1]*University of Alabama at Birmingham, BIRMINGHAM, United States of America*
[2]*Wakayama Medical University, WAKAYAMA, Japan*
[3]*University of Auburn, AUBURN, United States of America*

P3-018 **The pneumococcal pilus activates Toll-like receptor 2 and binds integrins**

Alan Basset[1], Cyril Benes[2], Sophie Forte[1], Nathaniel Johnson[1], Andrew Camilli[3], Richard Malley[4]

[1]*Children's Hospital, BOSTON, USA*
[2]*Beth-Israel Deaconess Medical Center, BOSTON, USA*
[3]*Tufts University School of Medicine, BOSTON, USA*

P3-019 **Enumerating pneumococcal 23F capsule specific B lymphocytes in HIV negative Malawian adults post vaccination by flow cytometry**

Herbert Longwe[1], Stephen Gordon[2], Rose Malamba[1], Neil French[1]

[1]*Malawi-Liverpool-Wellcome Trust Laboratories, BLANTYRE, Malawi*
[2]*Liverpool School of Tropical Medicine, LIVERPOOL, United Kingdom*

Symposium 10. Protein based pneumococcal vaccines

Chairs Richard Malley (USA) and David Briles (USA)

P3-020 **Recognition of pneumococcal isolates by antisera raised against PspA fragments from different clades**

Eliane Miyaji[1], Michelle Darrieux[1], Adriana Moreno[1], Daniela Ferreira[1], Fabiana Pimenta[2], Ana Lucia De Andrade[2], Luciana Leite[1]

[1]*Instituto Butantan, SAO PAULO, Brazil*
[2]*Instituto de Patologia Tropical e Saude Publica, Universidade Federal de Goias, GOIANIA, Brazil*

P3-021 **PspA Sequence Diversity Among Invasive And Non-Invasive Isolates In India**

Rajesh Verma, Seema Sood, Arti Kapil, Bimal Das

All India Institute of Medical Sciences, NEW DELHI, India

P3-022 **The Proline-rich region of Pneumococcal Surface Proteins A and C elicits antibody-mediated protection against pneumococcal infection**

Calvin Daniels, Patricia Coan, Janice King, Yvette Hale, David Briles, Susan Hollingshead

University of Alabama at Birmingham, BIRMINGHAM, AL, United States of America

Neuraminidase A (NanA) is essential for nasal colonization of mice with *Streptococcus pneumoniae* and recombinant enzymatically active or inactive NanA elicits almost complete protection against nasal colonization of mice.

Muneki Hotomi, «GreetingLine», Shaper Mirza, James M. Watt, «GreetingLine», Fredrik W. van Ginkel, Susan K. Hollingshead, and David E. Briles.

Other investigators have shown that pneumococcal neuraminidase A is important for pneumococcal colonization and otitis media in chinchillas and virulence following lung challenge in mice. Immunization with NanA has been reported to protect against sepsis and lung challenge in mice and against otitis media and colonization in chinchillas. Our data strongly support an important role for NanA in pneumococcal colonization of mice and their subsequent invasion into the brain. Our studies with mice have been reproducibly preformed with independent NanA mutants in more than one strain of *S. pneumoniae*. We have also shown that immunization with rNanA can provide virtually complete protection against colonization and subsequent infection of the olfactory bulbs and brain. Our immunization studies have used several NanA constructs. The smallest construct to elicit protection was 571 amino acids in size and retained neuraminidase activity. We also obtained protection with two single amino acid replacement mutants E647T and Y752F, neither of which exhibited neuraminidase activity. These findings indicate that NanA-mediated immune protection against colonization does not require an enzymatically active neuraminidase. Similar results have been published by Yesilkaya *et al*, (2006) showing that similar non-enzymatically active amino acid replacement mutants of NanA can elicit protection against lung challenge with pneumococci. Based on the data presented here NanA could be an important immunogen to be included in a vaccine designed to prevent pneumococcal colonization.